REMARKS

I. Support for Claim Amendments

The claims were amended to more clearly define the invention. Claim 1 was amended to correct indefinite claim language. Support for this amendment is found throughout the Specification, for example on pages 5-9, and 11-12. Claim 4 was amended in order to clarify what is meant by the term "modified." Support for this amendment can be found in the Specification, for example on page 5, lines 33-35, page 6, lines 10-14, page 8, lines 16-17, page 9, lines 24-25, and page 12, lines 4-7. Claims 12 and 14 were also amended in order to clarify indefinite claim language. Support for these amendments can be found in the Specification, for example on page 6, lines 10-14, page 8, lines 16-17, page 9, lines 24-25, page 12, lines 4-7, and Figures 1 and 2. Support for newly added claim 35 can be found throughout the Specification, for example on page 5, lines 26-34, pages 8-9, page 11, lines 14-35, page 12, lines 1-2, and Figures 1 and 2. Accordingly, no new matter is added by this Amendment and entry thereof is respectfully requested.

II. Objection to the Oath/Declaration

The Examiner objected to the oath or declaration because non-initialed and/or non-dated alterations had been made to the oath or declaration under 37 CFR §1.52(c). In order to overcome this objection, a supplemental application data sheet has been filed herewith in accordance with MPEP §§ 601.05(c) and (d) and 37 CFR §1.76(c).

III. Objection to the Drawings and Specification

The Examiner objected to the drawings and the specification because the specification contained two sets of different drawings. The figure set in which both Figure 1 and 2 are on the same sheet of paper, which have already been accepted and approved by the draftsperson, is the correct set of figures.

IV. Objection to Claim 7

The Examiner objected to claim 7 because of informality in the language of the claim. Applicants have amended this claim as suggested by the Examiner.

V. Rejection of claims 1-22, 26, and 30-34 under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-22, 26, and 30-34 as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Examiner rejected claim 1 (2-22, 26 and 30-34 dependent on), because the language "for recombinant DNA expression" is an intended use of the claimed host cell and has no patentable weight with respect to the claimed product, which is the host cell comprising a *Flavobacterium heparinum*. Applicants have amended claim 1 to correct this indefinite claim language. Withdrawal of the rejection is respectfully requested.

The Examiner also rejected claim 4 as being indefinite because it was unclear what was intended by Applicants to be encompassed by a "modified broad-host plasmid." Applicants have amended claim 4 to clarify what is meant by the term "modified." Withdrawal of the rejection is respectfully requested.

The Examiner rejected claim 12 as being indefinite noting that it is unclear what applicants intended to be encompassed by a "heparinase I gene regulatory region." Applicants respectfully traverse the rejection as one having ordinary skill in the art would know what is encompassed by this term. Nevertheless, Applicants have amended claims 12 and 14 to clarify that the regulatory region is the *hepA* or *lysA* promoter. Withdrawal of the rejection is respectfully requested.

In addition, the Examiner rejected claim 22 as being indefinite because it was unclear what Applicants intended to be encompassed by "*hepA*." Applicants respectfully traverse the rejection as one having ordinary skill in the art would know what is encompassed by this term. Nevertheless, Applicants have amended claim 22 to clarify the meaning of the claim term, "*hepA*." In addition, page 4, lines 6-8 of the specification describes the *hepA* gene as coding for heparinase I and being a homologous gene to *Flavobacterium heparinum*. Furthermore, page 8, lines 16-17 of the specification describe the *hepA* promoter as an 830 bp fragment of the 5' end of the *hepA* gene, which is induced by heparin. Withdrawal of the rejection is respectfully requested.

VI. Rejection of claims 1-22, 26, and 30-34 under 35 U.S.C. § 112, first paragraph

Claims 1-22, 26, and 30-34 are rejected under 35 U.S.C. § 112, first paragraph, as the claims allegedly contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states that the claims are directed to all possible transformed *Flavobacterium heparinum* host cells comprising any vector, wherein said vector is any broad-host plasmid. The Examiner asserts that the

specification only provides a single representative species of transformed *Flavobacterium heparinum* host cells (i.e., transformed with pIBFX1 and PIBFX2) encompassed by these claims. The Examiner concludes that, given the lack of additional representative species as encompassed by the claims, Applicants have failed to specifically describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

The Examiner also asserts that the specification, while being enabling for *Flavobacterium heparinum* transformed with pIBFX1 and pIBFX2, does not reasonably provide *Flavobacterium heparinum* transformed with any vector. The Examiner alleges that the specification does not support the broad scope of the claims which encompass all modifications of any vector because the specification does not establish; (A) regions of the vector structure which may be modified without effecting its activity; (B) the general tolerance of any vector to modification and extent of such tolerance; (C) a rational and predictive scheme for modifying any nucleic acid residue of any vector with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. The Examiner asserts that it would require undue experimentation for one skilled in the art to arrive at the majority of those transformed *Flavobacterium heparinum* of the claimed genus.

Applicants respectfully traverse the rejection. Applicants assert that the specification includes a sufficient description of a variety of proteins and selectable markers, which were successfully expressed in the *Flavobacterium heparinum* host cell. Applicants also assert that, given the disclosure in the specification, one skilled in the art would be able to use various vectors and express different proteins without undue experimentation.

In analyzing the adequacy of the written description, it is determined if the description clearly allows persons of ordinary skill in the art to recognize that the inventor invented what is claimed. *See In re Gosteli*, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). Additionally, "[t]he entire claim must be considered, including the preamble language and the transitional phrase." *Manual of Patent Examining Procedure* § 2163 (2001). Applicants assert that the specification includes a sufficient description of the various proteins and selectable markers, which were successfully expressed in the *Flavobacterium heparinum* host cell. Contrary to the assertions in the Office Action that "the specification only provides a single representative species of transformed *Flavobacterium heparinum* host cells," as discussed on page 11, line 14 to page 12, line 2, and Figures 1 and 2, numerous homologous and heterologous proteins and selectable markers were successfully expressed in the *Flavobacterium heparinum* host cell including chondroitinase AC, chondroitinase B, heparinase II, heparinase III, heparinase I, the *lacZ* gene, the trimethoprim resistance gene, *dhfrII*, and the *bla* gene conferring ampicillin resistance. The description clearly allows persons of ordinary skill in the art to recognize that the inventor invented what is claimed, a new host system for expressing recombinant DNA.

Additionally, given the guidance in the specification, other such proteins and selectable markers may be used by the skilled artisan by routine methods available in the art and described in the specification without undue experimentation. For example, page 5, line 13 to page 6, line 2 of the specification describes the characteristics of a useful vector that can be inserted into *Flavobacterium heparinum* host cells. For instance, the specification states on page 5, lines 32-35, that the selective marker is preferably regulated by a regulatory region from *F. heparinum* such as the heparinase I gene regulatory region. Furthermore, other useful plasmids and the genetic engineering methods for inserting genes of interest into these plasmids will be apparent

to those of ordinary skill in the art without undue experimentation. For instance, general techniques for the construction of a vector and nucleic acid manipulation are described generally, for example, in Sambrook et al., "Molecular Cloning: A Laboratory Manual", Vols. 1-3 (Cold Spring Harbor Laboratory Press, 2 ed., 1989) or in Ausubel et al., Current Protocols in Molecular Biology (Green Publishing and Wiley-Interscience: New York, 1987).

Therefore, the description clearly enables persons of ordinary skill in the art to practice the claimed invention without undue experimentation. Also, as discussed above, the description clearly allows persons of ordinary skill in the art to recognize that the inventor invented what is claimed, a new host system for expressing recombinant DNA. Withdrawal of the rejection of claims 1-22, 26, and 30-34 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

VII. Rejection of claims 1, 5-8 and 13-18 under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1, 5-8 and 13-18 under 35 U.S.C. § 102(b) as being anticipated by Zimmerman et al. (WO 96/01894, January 25, 1996). Zimmerman et al. is relied on in the Action for teaching the culturing of *Flavobacterium heparinum*, and the isolation and cloning of the genes encoding the enzymes, chondroitinase AC and chondroitinase B, from *Flavobacterium heparinum*. This rejection is respectfully traversed for the following reasons.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). "Every element of the claimed invention must be literally present, arranged as in the claim" for an invention to be anticipated. *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989).

Zimmerman et al. teach the isolation and cloning of the genes encoding the chondroitinase AC and chondroitinase B enzymes from *Flavobacterium heparinum*. However, Zimmerman et al. teaches the cloning of these genes in *E. coli* only. There is no teaching of how to use *Flavobacterium heparinum* as a host system. Even if the use of *Flavobacterium heparinum* as a host system may have been suggested by the reference, it was not an enabling disclosure. In order to anticipate under §102(b), a prior art reference must be enabling to a person having ordinary skill in the art. See *Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 62 USPQ2d 1865 (Fed. Cir. 2002); *Bristol-Myers Squibb Co. v. Ben Venue Laboratories*, Inc., 246 F.3d 1368, 1374, 58 USPQ2d 1508 (Fed. Cir. 2001) ("To anticipate, the reference must ... enable one of skill in the art to make and use the claimed invention.") Zimmerman et al. only provides an enabling disclosure for the use of *E. coli* as a host system for the *F. heparinum* genes. Therefore, there is no teaching of the use of *Flavobacterium heparinum* as a host system for recombinant DNA. Moreover, Applicants respectfully point out that claims 30 and 32-35 recite preferred recombinant DNA constructs neither taught nor suggested by Zimmerman et al. Withdrawal of the rejection of claims 1, 5-8 and 13-18 under 35 U.S.C. § 102(b) over Zimmerman et al. is respectfully requested.

VIII. Rejection of claims 1-11, 13-21, 26 and 30-34 under 35 U.S.C. § 103(a)

Claims 1-11, 13-21, 26 and 30-34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zimmerman et al. (WO 96/01894, January 25, 1996) and McBride et al. (Applied and Environmental Microbiology, Vol. 62, No. 8, pages 3017-3022, August 1996). Zimmerman et al. is relied on in the Action for teaching the culturing of *Flavobacterium heparinum*, and the isolation and cloning of the genes encoding the enzymes, chondroitinase AC

and chondroitinase B, from *Flavobacterium heparinum*. Zimmerman et al. is further relied upon to teach that the cloned genes can be used in the conjunction with suitable expression systems to produce enzymes in *Flavobacterium*, for example, under the control of overexpression promoters, or in organisms other than *Flavobacterium*. McBride at al. is relied on in the Action for teaching the development of techniques to genetically manipulate members of the genera *Flavobacterium*. McBride et al. is further relied on in the Action to teach that Tn4351 transposon DNA can be transferred from *E. coli* to *Flavobacterium meningosepticum*. The Examiner concludes that one of ordinary skill in the art at the time of the filing would have been motivated to express the genes encoding the *Flavobacterium heparinum* enzymes, chondroitinase AC and chondroitinase B, in *Flavobacterium heparinum* under the control of an overexpression promoter in a suitable expression system, such as the tn4351 transposon DNA, as taught by McBride at al. and suggested by Zimmerman et al. Applicants respectfully traverse this rejection.

As discussed above for the § 102(b) rejection, Zimmerman et al. teach the isolation and cloning of the genes encoding the chondroitinase AC and chondroitinase B enzymes from *Flavobacterium heparinum*. However, Zimmerman et al. teach the cloning of these genes in *E. coli* only. There is no teaching of how to use *Flavobacterium heparinum* as a host system for these or any other genes. Zimmerman et al. contains one sentence which states that the cloned genes encoding chondroitinase AC and chondroitinase B can be used in conjunction with suitable expression systems to produce the enzymes in *Flavobacterium*, for example, under the control of overexpression promoters, or in organisms other than *Flavobacterium*. However, the remainder of the reference discusses how the inventors were able to create *Flavobacterium heparinum* gene libraries in *E. coli* as well as express chondroitinase AC and chondroitinase B in

E. coli, with no mention of any attempted or successful expression in *Flavobacterium heparinum*.

To properly make a rejection under 35 U.S.C. § 103, the Examiner has the initial burden of establishing a *prima facie* case of obviousness. Meeting this burden requires the Examiner to show first that the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process. Second, the Examiner must establish that the prior art would have revealed that in carrying out the process, those of ordinary skill in the art would have had a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Since Zimmerman et al. provides no details on how to use *Flavobacterium heparinum* as a host system, Applicants submit that those of ordinary skill in the art would not have had a reasonable expectation of success in using this host system merely because of one sentence in the prior art which mentioned it as a possibility.

McBride at el. teaches the introduction of the transposon Tn4351 into the *Flavobacterium meningosepticum* chromosome via conjugation. McBride et al. also teaches mutagenesis of the Tn4351 transposon in order to isolate autotrophic mutants of *Flavobacterium meningosepticum*. However, there is no teaching in McBride et al. of the transformation of a *Flavobacterium heparinum* host cell with a recombinant DNA construction effective to cause expression of a protein coded by a homologous or heterologous coding sequence placed under the control of a regulatory region effective in *Flavobacterium heparinum*, as claimed by the amended claims of this application. Although McBride at al. teaches that the Tn4351 transposon is able to insert itself into the chromosome of *Flavobacterium meningosepticum*, there is no teaching of the isolation of a particular protein-encoding nucleotide sequence, the insertion of

this sequence into a vector, the insertion of a regulatory region into the vector so that it controls the expression of this nucleotide sequence, and the subsequent transformation of this vector into the *Flavobacterium* so that the homologous or heterologous protein may be expressed as desired (i.e. by overexpression promoters, by sequences that regulate the post-translation characteristics of the proteins, etc.)

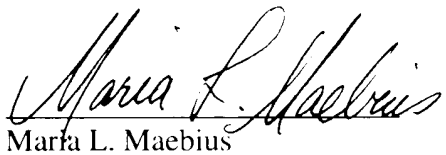
The Examiner believes it would have been obvious to express the genes encoding the *Flavobacterium heparinum* enzymes, chondroitinase AC and chondroitinase B, in *Flavobacterium heparinum* under the control of an overexpression promoter in a suitable expression system, such as the tn4351 transposon DNA, as taught by McBride at al. and suggested by Zimmerman et al. However, the tn4351 transposon alone is not a suitable expression system for the invention claimed here. McBride et al. does not teach any method with which to insert recombinant DNA sequences into the transposon itself so that desired proteins may be expressed in the *Flavobacterium* host. McBride et al. simply teaches the insertion of the tn4351 transposon into the chromosome of the *Flavobacterium* so that this transposon can be subjected to mutagenesis in order to produce different phenotypes of the bacteria. There is no teaching or suggestion of using *Flavobacterium heparinum* as a host cell for the expression of desired proteins at regulated rates and with particular characteristics. Furthermore, as stated above, Zimmerman et al.'s brief, non-enabling reference to the use of *Flavobacterium heparinum* as a host system would not have provided any motivation to combine this reference with McBride et al., which is focused on a different purpose. Moreover, Applicants respectfully point out that claims 30 and 32-35 recite preferred recombinant DNA constructs neither taught nor suggested by Zimmerman et al. or McBride et al.

Accordingly, Applicants assert that none of the references, whether alone or in combination, teach or suggest the presently claimed invention. Applicants respectfully request that the rejection be withdrawn.

IX. CONCLUSION

In view of the foregoing remarks, Applicants believe that the application is in condition for allowance. However, if the Examiner disagrees, he is encouraged to call the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,



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